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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,293	FREYMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2007 and 16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-27 and 29-41* is/are pending in the application.

4a) Of the above claim(s) *3,4,16-26,29,31-34 and 36-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-15, 27, 30 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed on 1/25/07 and 10/16/06 were entered.

Claims 1, 3-27, 29-41 are pending in the present application.

Applicants elected previously Group I, drawn to a method for producing a decellularized extracellular matrix material containing a biological material or for producing a tissue regeneration scaffold for implantation into a patient wherein the step of conditioning a body tissue of a donor animal by genetic engineering and allowing the conditioned body tissue to produce the biological material are conducted prior to harvesting the conditioned body tissue from the donor animal. Applicants further elected the following species with traverse in the reply filed on 9/19/05, (a) bone marrow as a species of a body tissue; (b) VEGF as a species of a biological material; and (c) human as a species of a donor animal.

Claims 3-4, 16-26, 29, 31-34 and 36-41 were withdrawn previously from further consideration because they are directed to non-elected inventions.

Accordingly, amended claims 1, 5-15, 27, 30 and 35 are examined on the merits herein with the aforementioned elected species.

Response to Amendment

The Notice to comply issued on 1/8/07 was withdrawn.

Upon further consideration, the rejection under 35 U.S.C. 112, first paragraph, for enablement was withdrawn.

The rejection under 35 U.S.C. 102(b) as being unpatentable over Naughton (US 5,830,708; IDS) was withdrawn in light of Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 13 recites the

broad recitation **"cell binding domain",** and the claim also recites **"(e.g., RGD)"** which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 5, 9 and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Vituri et al. (Brazilian Journal of Medical and Biological Research 33:889-895, 2000). ***This is a new ground of rejection.***

Vituri et al disclosed a method in which 2-month old male Swiss mice were submitted to protein malnutrition with a low-protein diet containing 4% casein (conditioning body tissue of a donor animal) as compared to 20% casein in the control diet, and when the treated mice had attained a 20% loss of their original body weight, extracellular matrix (ECM) proteins from bone marrow were extracted (a decellularization condition) and it was determined that bone marrow ECM from undernourished mice had greater amounts of extractable fibronectin and laminin (biological materials) compared to the control animals (see at least the abstract). Vituri

et al taught that bone marrow ECM was obtained from the femurs of the mice, aspirated into a buffer, centrifuged at 2,500 for 15 minutes and the ECM/soluble protein containing supernatant was recovered (see at least page 890, col. 2, last two paragraphs).

Accordingly, the teachings of Vituri et al meet every limitation of the claims as written. Therefore, the reference anticipates the instant claims.

Claim 35 is rejected under 35 U.S.C. 102(e) as being anticipated by Mitchell et al (US 2002/0115208). ***This is a new ground of rejection.***

Mitchell et al disclosed methods for producing scaffolds for use in tissue engineering and for producing tissue engineered constructs and engineered tissues for implantation into the body (see at least the abstract; Summary of the Invention). Mitchell et al taught at least a method in which a substrate (e.g., a biocompatible polymer) is seeded with a first population of cells (obtained from a donor) known to secrete extracellular matrix molecules, cells are maintained in culture for a growth period and during this growth period mechanical or electrical stimuli or selected biological active agents (e.g., growth factors) are applied, after which the construct is decellularized and the decellularized tissue engineering construct (scaffold) consisting primarily of extracellular matrix components such as collagen and elastin, and optionally the substrate that was initially seeded is substantially or entirely removed from the scaffold (at least paragraphs 14-17, 68-71; 85). Similarly for engineered native tissues, the native tissue from an animal or human donor is harvested, subjecting the native

tissue tone or more tissue engineering steps (e.g., seeding the native tissue with cells and maintaining the seeded tissue for a growth period during which stimuli can be applied) and decellularizing the engineered tissue (paragraph 22). Mitchell et al also taught that cells obtained from a donor or from an established cell line have been genetically manipulated to produce scarce but desirable proteins such as elastin (bottom of paragraph 85). Mitchell et al further taught that although in general production of the tissue engineered construct involves culturing the developing tissue primarily *in vitro*, tissue engineered constructs produced at least in part by culturing the tissue *in vivo* are also contemplated (col. 5, bottom of paragraph 67).

It is noted that the term "body tissue" is defined by the instant specification broadly encompasses any or a number of cells, tissues or organs (see page 7, lines 7-8); and as written and contemplated by Applicants the recited steps (a)-(e) in claim 35 are not necessarily in a consecutive sequence (please refer to original claims 1-3). Therefore, the teachings of Mitchell et al (US 2002/0115208) meet every limitation of the claim as broadly written. Thus, the reference anticipates the instant claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended claims 1, 5, 8-15, 27 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS). ***This is a new ground of rejection necessitated by Applicant's amendment.***

With respect to the elected species, Naughton teaches a method for producing a composition containing naturally secreted human extracellular matrix material, said method comprises the steps of: (a) culturing extracellular matrix secreting human stromal cells from tissues/organs obtained by appropriate biopsy or upon autopsy, including aspirated bone marrow from normal human adult volunteers (col. 5, lines 48-54; col. 15, lines 7-9), on a biocompatible three dimensional framework *in vitro*; (b) the stromal cells are killed after secretion of the extracellular matrix onto the framework and the cells and cellular contents are removed from the framework (col. 11, line 62 continues to line 63 of col. 12); (c) the extracellular matrix material deposited on the framework is collected and further processed to obtain a physiologically acceptable composition (col. 12, line 66 continues to line 20 of col. 14). Naughton further teaches that it may be desirable to prepare an extracellular matrix containing a foreign gene product, growth factor, regulatory factor and in such a situation the cells are genetically engineered to express the gene product that is immobilized in the extracellular matrix laid down by the stromal cells (col. 10, line 59 continues to line 22 of col. 11). This is a conditioning step. Naughton teaches that preferably, the expression control elements used should allow for the regulated expression of the gene so that the product can be over-synthesized in culture (col. 11, lines 15-17). Furthermore, Naughton teaches that

biologically active substances such as proteins and drugs can also be incorporated in the composition for release or controlled release of these active substances after injection of the composition that include tissue growth factors such as TGF-beta and the like which promote healing and tissue repair at the site of injection (col. 13, lines 12-22). Naughton teaches that the extracellular matrix preparation is capable of promoting connective tissue deposition, angiogenesis, reepithilialization and fibroplasias, which is useful in the repair of skin and other tissue defects, and that the preparation is used to repair tissue defects by injection at the site of the defect (col. 3, lines 43-48; col. 13, line 43 continues to line 20 of col. 14). It should be noted that the term "body tissue" is defined by the instant specification broadly encompasses any or a number of cells, tissues or organs (see page 7, lines 7-8).

Naughton does not specifically teach a method for producing a decellularized extracellular matrix containing a biological material, comprising the step of conditioning (genetic engineering is the elected invention) a body tissue (bone marrow is the elected species) of a donor animal (human is the elected species) to produce the biological material **prior to the step of harvesting the conditioned body tissue from the donor animal and decelluarizing the conditioned body tissue**.

However, at the effective filing date of the present application Mitchell et al also disclosed methods for producing decellularized tissue engineered constructs and decellularized engineered native tissues for implanting into an individual in need thereof (see at least the abstract; Summary of the Invention), and taught that although in general production of the tissue engineered construct involves culturing the developing

tissue primarily *in vitro*, **tissue engineered constructs produced at least in part by culturing the tissue *in vivo* are also contemplated** (col. 5, bottom of paragraph 67). Mitchell et al further taught that there is a need to **expose developing tissue engineered constructs to certain stimuli, so that the resulting construct develops properties and structure that more closely resemble those of the corresponding naturally occurring tissue** (paragraph 96).

Patel et al also taught a process for preparing acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* (see at least Summary of the Invention). Patel et al further disclosed that **the acellular collagen-containing extracellular matrices can be derived from renal capsular tissues harvested from either transgenic animals (pre-conditioned donor animal) or non-transgenic animals**, and that animals encompass mammals, preferably porcine, bovine or ovine (col. 3, lines 11-21).

Wolff et al also disclosed **a process for delivering a polynucleotide encoding a protein of interest (e.g., hormones, cytokines, growth factors and others) into parenchymal cells within tissues *in situ* and *in vivo*, including parenchymal cells of bone marrow within a mammal** (see at least Summary of the Invention; and page 8, second paragraph; page 7, first paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the method of Naughton by also preparing a decellularized bone marrow extracellular matrix material harvested from the bone marrow of a donor animal, including a human donor, whose parenchymal cells of the bone marrow have been

transfected with a polynucleotide encoding a protein of interest in light of the teachings of Mitchell et al., Patel et al. and Wolff et al. as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modification because acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* has been taught by Patel et al can be harvested from a transgenic animal. Additionally, Mitchell et al also taught the preparation of decellularized tissue engineered constructs and/or decellularized engineered native tissues, wherein the tissue engineered constructs can be produced at least in part by culturing the tissue *in vivo*. Moreover, unlike the decellularized extracellular matrix prepared *in vitro* or in cultured conditions, the conditioned bone marrow extracellular matrix to be harvested from a donor animal has been subjected to the same physiological conditions as a naturally occurring bone marrow. Furthermore, Wolff et al already disclosed successfully a process for delivering a polynucleotide encoding any protein of interest in parenchymal cells of bone marrow within a mammal.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton, Mitchell et al., Patel et al., and Wolff et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 13 (VEGF embodiment) and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS) as applied to claims 1, 5, 8-15 and 27 above, and further in view of Herlyn et al. (WO 98/39035; Cited previously). ***This is a new ground of rejection.***

The combined teachings of Naughton, Mitchell et al., Patel et al. and Wolff et al. were presented above. However, none of the references teaches specifically that bone marrow is transfected with a nucleic acid encoding VEGF.

However, at the effective filing date of the present application Herlyn et al already teach growth factors, particularly VEGF is useful in wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis and *ex vivo* method for infecting tissue to be transplanted with a recombinant virus expressing VEGF prior to transplantation (at least page 6, lines 14-23).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the combined method of Naughton, Mitchell et al., Patel et al. and Wolff et al. by also selecting VEGF as an foreign gene product to be incorporated into the decellularized extracellular matrix in light of the teachings of Herlyn et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Herlyn et al already teach growth factors, particularly VEGF is useful in wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis, and that this

would enhance the clinical value for the composition containing the decellularized extracellular matrix material resulting from the combined teachings of Naughton, Mitchell et al., Patel et al. and Wolff et al.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton, Mitchell et al., Patel et al. Wolff et al., and Herlyn et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379) as applied to claims 1, 5, 8-15 and 27 above, and further in view of Schwarz et al. (US 6,656,916). ***This is a new ground of rejection.***

The combined teachings of Naughton, Mitchell et al., Patel et al. and Wolff et al. were presented above. However, none of the references teaches specifically that a further step of delivering a therapeutic agent to the body tissue before or after the conditioning step.

However, at the effective filing date of the present application, Schwartz et al already taught **a method of increasing the cellular expression of a gene in a biological tissue in an animal, including a bone marrow in a human**, said method

comprises administering to said animal a pharmacologically effective dose of a glucocorticoid in an amount sufficient to increase the cellular expression of said gene (see at least col. 2, lines 35-51; col. 5, lines 54-59). Schwartz et al taught specifically that any glucocorticoid such as hydrocortisone, prednisone, prednisolone, triamcinolone, betamethasone, budesonide, flunisolide and dexamethasone can be used (col. 5, lines 31-37). The glucocorticoid may be administered concurrently with the delivery of the gene, **prior to the delivery of the gene or after delivery of the gene** (col. 5, lines 48-51).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the combined method of Naughton, Mitchell et al., Patel et al. and Wolff et al. by also administering to the donor animal a therapeutic agent such as a glucocoritoid to a body tissue prior to or after the gene delivery in light of the teachings of Schwarz et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the administration of a therapeutic agent such as a glucocorticoid prior to or after the delivery of a gene would enhance the cellular expression of a delivered gene in a biological tissue, including a bone marrow in a human, as taught by Schwartz et al.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton, Mitchell et al., Patel et al. Wolff et al., and Schwarz et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D.
PRIMARY EXAMINER